IV. AMENDMENT TO THE DRAWINGS

Please replace Figure 5a with the replacement formal Figure 5A submitted herewith.

VI. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based upon the following amendment and following remarks are respectfully requested. Claims 29-56 are currently pending and at issue in this application. This response is timely filed with a three-month extension of time.

In paragraph 2 of the official action, the examiner requested that the application be reviewed for all spelling and trademark errors. The applicants respectfully submit that this request has been fulfilled.

In paragraph 6 part A of the official action, the examiner objected to claims 42 and 56 for failing to recite the word "antibody" after the words anti-TNFα, anti-CD54, anti-CD11, anti-CD11a, and anti-IL-1. The applicants have amended claims 42 and 56 by inserting the word "antibody" after the words the appropriate molecules.

In paragraph 6, part B of the official action, the examiner objected to claims 29-42, 50 and 51 for the recitation "CD80 antigen." The examiner alleged that this phrase lacked clarity or consistency. The applicants have removed the word "antigen" from the phrase "CD80 antigen" and submit that the objection has been overcome and should be withdrawn.

The applicants have discovered two errors in the sequence of the 16c10 light chain antibody as show in Figure 5a. In view of this discovery, the applicants are submitting a substitute Sequence Listing and a formal replacement Figure 5a, both of which set forth the correct sequence of the 16c10 light chain antibody. The substitute Sequence Listing also amends a typographical error in the nucleotide and amino acid sequence of the 7c10 heavy chain and the 16c10 heavy chain. Specifically, nucleotides 58-60 of SEQ ID NO: 2 (the heavy chain 7c10 nucleotide and amino acid sequences) has been changed from a "gag" to a "cag" while the corresponding amino acid at position 20 has changed from a "Glu" (glutamate) to a "Gln" (glutamine). Nucleotides 523-525 of SEQ ID NO: 6 (the heavy chain 16c10 nucleotide and amino acid sequence) has been changed from a "ctc" to a "gtc" while the corresponding amino acid at position 175 has changed from a "Leu" (leucine) to a "Val" (valine). Both of these amendments to SEQ ID NOS: 2 and 6 were typographical errors and do not contain new matter. Support for the amendment to SEQ ID NOS: 2 and 6 can be

found in originally filed Figures 3B (7c10 heavy chain nucleotide and amino acid sequence) and 5B (16c10 heavy chain nucleotide and amino acid sequence) respectively.

The applicants have also amended SEQ ID NO: 5. SEQ ID NO: 5 shows the nucleotide and amino acid sequences for the light chain 16c10 antibody. In SEQ ID NO:5, the nucleotide nos. 67-69 have been changed from "gtc" to "gcc" while the corresponding amino acid has changed from "Val" (valine) to "Ala" (alanine). Nucleotide nos. 412-414 have been changed from "tcg" to "acg" while the corresponding amino acid has changed from a "Ser" (serine) to a "Thr" (threonine). The applicants, through their undersigned attorney, hereby state that the nucleotide and amino acid sequences of the 16c10 light chain of ATCC Deposit Accession No. HB-12119 (deposited with ATCC on May 29, 1996) is the same as the sequence filed in the substitute Sequence Listing submitted herewith and do not constitute new matter. If necessary, a declaration from the applicants will be submitted attesting that the newly amended 16c10 light chain sequence is identical to the sequence deposited with the American Type Culture Collection. Support for the 16c10 hybridoma can be found in the specification at page 61, lines 10-17 of the specification (as submitted by amendment November 4, 2004). Copies of the amended Sequence Listing in paper form and computer readable form for the above-identified application are attached hereto, in compliance with 37 C.F.R. §§ 1.821-1.825.

Pursuant to 37 C.F.R §1.821(f) and (g), the applicants, through the undersigned attorney, hereby state that the sequence listing information of the attached copies of the Sequence Listing in paper and computer readable form are the same and do not contain new matter.

The applicants hereby further submit a replacement sheet of Figure 5A that is labeled "Replacement Sheet" along with a marked-up copy of Figure 5A as required by 37 C.F.R. §121(d). In Figure 5A, the applicants have (1) replaced "V" (valine) at amino acid position no. 23 with an "A" (alanine); (2) replaced "T" (thymine) at corresponding nucleotide position no. 68 with an "C" (cytosine); (3) replaced "S" (serine) at amino acid position no. 138 with a "T" (threonine); and (4) replaced "T' (thymine) at corresponding nucleotide position no. 412 with an "A" (adenine). The applicants submit that replacement Figure 5a does not constitute new matter because support for the correct light chain 16c10 nucleotide and amino acid sequences can be found the in the ATCC deposit, which was deposited with ATCC on May 29, 1996 and this information can be found in the specification at page 61,

lines 10-17 of the specification (as submitted by amendment November 4, 2004). Copies of the replacement drawing Figure 5A for the above-identified application are attached hereto, in compliance with 37 C.F.R. § 1.85. Finally, the applicants have also amended the deposit information in the specification at page 61, line 10 by adding that hybridoma 7B6 was also deposited with hybridomas 7C10 and 16C10 on May 29, 1996 with the American Type Culture Collection. The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §112, Second Paragraph

In paragraph 5 of the official action, the examiner rejected claims 29-42 and 55 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. Specifically, the examiner alleged that the phrase "inhibiting or preventing T cell/B cell interactions associated with B cell lymphoma" are ill-defined because it is not clear whether the targeted patient population is a patient with B cell lymphoma or patient populations other than those with B cell lymphoma. The examiner further asserted that this phrase is further unclear as to whether the claims read on a patient with B cell lymphoma and one is inhibiting/preventing T cell/B cell interactions associated with the B cell lymphoma. Finally, the examiner alleged that this phrase is indefinite because the claimed methods do not require that the anti-CD80 antibodies need to be administered to a patient with B cell lymphoma. The examiner further rejected claims 41 and 55 as indefinite for the phrase "fragment thereof" as it was unclear whether anti-CD28 antibodies was being modified or whether fragment thereof meant to modify IL-17, IL-10, CTLA4-Ig and/or soluble CTLA-4.

Amended claim 29 is directed to a method for treating B cell lymphoma comprising administering an amount of a monoclonal anti-CD80 antibody or a CD80-binding fragment thereof sufficient to inhibit the binding of B cells and T cells via the CD80/CD28 pathway; wherein said monoclonal antibody or fragment thereof binds specifically to CD80 without inhibiting the binding of CD80 to CTLA-4. The applicants submit that amended claim 29 is clearly directed to treating a patient with B cell lymphoma using anti-CD80 antibodies or a fragment thereof that bind the CD80 receptor. Dependent claims 30-40 have all the limitations of amended claim 29 and thus are no longer indefinite as to the method for treating B cell lymphoma.

Amended claims 41 and 55 are directed to the method of either claim 29 or 43, wherein said anti-CD80 antibody or CD80-binding fragment thereof is administered in combination with an anti-CD28 antibody or a fragment thereof. The applicants submit that the phrase "fragment thereof" has proper antecedent basis and modifies anti-CD28 antibody. In view of the foregoing amendment and remarks, the applicants submit that the rejection of claims 29-42 and 55 under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §112, First Paragraph

Enablement

In paragraph 4, the examiner rejected claims 29-42, 50, 55, and 56 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written descriptive support to enable one of skill to make or use the invention.

Claims 29-42—Preventing T cell/B cell Interaction Associated with B cell Lymphoma

With regards to claims 29-42, the examiner alleged that the skilled artisan does not readily treat nor predict treatment of B cell lymphomas by preventing B cell lymphoma growth by preventing B and T cell interactions. The examiner further alleged that there is a lack of *in vivo* clinical data reflecting preventing T cell/B cell interaction associated with B cell lymphoma in the context of preventing B cell lymphoma. The examiner further asserted that diagnosis is required to differentiate between the different types of lymphomas, leukemias, and other causes of lymphadenopathy to give a proper prognosis for treatment of lymphomas. The examiner concluded that a skill artisan would not be able to predict preventing the occurrence of B cell lymphomas, but can only treat a B cell lymphoma after its presence is diagnosed.

As discussed above, amended claim 29 is directed to a method for treating B cell lymphoma comprising administering an amount of a monoclonal anti-CD80 antibody or a CD80-binding fragment thereof sufficient to inhibit the binding of B cells and T cells via the CD80/CD28 pathway, wherein said antibody or fragment thereof binds specifically to CD80 without inhibiting the binding of CD80 to CTLA-4. The applicants submit that the enablement of preventing B cell lymphoma using the anti-CD80 antibody taught in the specification is moot. The applicants submit, however, that a skilled artisan would be able to treat B cell lymphoma using the teachings of the specification. Specifically, the applicants

submit that specification teaches that anti-CD80 antibody binds to B7.1, which is highly expressed in B cell lymphoma cells. This binding prevents T cells from interacting with B cell lymphoma cells and prevents co-stimulation of T cells and B cells. Accordingly, blocking this interaction by using anti-CD80 antibody can be used to treat B cell lymphoma. Claims 30-42 are dependent upon claim 29 and thus drawn the same limitations. In view of the foregoing amendment and remarks, the applicants respectfully submits that the rejection of claims 29-42 under 35 U.S.C. §112, first paragraph, regarding the enablement of preventing B cell lymphoma is moot and should be withdrawn.

Claims 41, 42, 55, and 56—Combination Therapy with Immunomodulators and Immunosuppressants

In paragraph 4B of the official action, the examiner alleged that claims 41, 42, 55, and 56 lacked enablement because the skilled artisan would not necessarily predict that inhibiting immune responses would be in the best interest of treating a B cell lymphoma patient. Specifically, the examiner asserted that a skilled artisan would prefer to maintain the health and immune status of a cancer patient and not to immunosuppress the patient. The examiner pointed to Weiner *et al., Expert Opinion Biol.*, 4:375-385 (2004; enclosed herein) as evidence that none of the immunomodulators or immunosuppressants recited in the claims are described in the contest of treating lymphoma as a combinational therapy with monoclonal antibodies to treat lymphomas. The examiner further asserted that other types of B cell lymphoma treatments (*i.e.*, anti-LFA1 and anti-ICAM antibodies used to inhibit LAK cell cytotoxicity *citing* Mehta *et al., Cellular Immunology* 155:95-110 (1994)) do not use immunomodulators or immunosuppressants. The examiner alleged that inhibiting immune responses in a cancer patient would serve in aiding the treatment of B cell lymphoma in combination with anti-CD80/anti-B7.1 antibodies. The examiner concluded that undue experimentation would be required absent a specific detailed discussion in the applicants specification, or working examples teaching the combination of immunomodulators/immunosuppressants with anti-CD80 antibodies to treat B-cell lymphomas.

Solely to expedite prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have canceled claims 42 and 56. Amended claims 41 and 55 are now directed to the method of claim 29, wherein said anti-CD80 antibody or a CD80-binding fragment thereof is administered in combination with an

anti-CD28 antibody, and a fragment thereof. In view of the foregoing amendment, the applicants submit that undue experimentation would not be required to practice a method administering anti-CD80 antibody or CD80-binding fragment in combination with an anti-CD28 antibody, and a fragment thereof. Amended claims 41 and 55 satisfies the "how to make" prong of the enablement requirement because the immunomodulators anti-CD28 antibody is used in combination therapies for the targeting and treating of B cell lymphoma. Specifically, anti-CD28 antibody was found to effective in other combinational therapies for treating lymphoma (*see* second column, first paragraph on page 142 of Kipriyanov *et al., J. of Immunology* 169:137-144 (2002)). Accordingly, the applicants submit that undue experimentation would be required by combining anti-CD80 antibody with anti-CD28 antibody to treat B cell lymphoma. In view of the foregoing amendments and remarks, the applicants respectfully submit that the rejection of claims 41, 42, 55, and 56 under 35 U.S.C. §112, first paragraph, for lack of enablement has been overcome and should be withdrawn.

Claims 36 and 50: Deposit of the 7C10 and 16C10 Antibodies

In paragraph 4C of the official action, the examiner rejected claims 36 and 50 under the enablement requirement because there is no indication in the specification as to the public availability of the 7C10 and 16C10 antibodies. The examiner further asserted that without this public availability, one of skill would be unable to use these antibodies.

In a preliminary amendment filed November 4, 2004, the applicants added a paragraph at line 10, page 61 of the specification indicating the public availability of the hybridoma 7C10 and hybridoma 16C10, which produce antibodies 7C10 and 16C10 as required by the Budapest Treaty. In further support of these biological deposits, the applicants hereby submit a declaration of biological deposit pursuant to the Budapest Treaty. In view of the foregoing submission and remarks, the applicants submit that the rejection of claims 36 and 50 under 35 U.S.C. §112, first paragraph, for lacking an enabling deposit has been overcome and should be withdrawn.

Rejection Pursuant to Non-Statutory Obviousness Double Patenting

In paragraph 8 of the official action, the examiner provisionally rejected claims 29-56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-26, 32, and 37 of co-pending application U.S. Patent Appl. No. 09/758,173. Specifically, the examiner alleged that both sets of claims are directed to the

same or nearly the same methods of treating B cell lymphoma with the same CD80-specific antibodies that inhibit the binding of B cells and T cells via the CD80/CD28 pathway.

The applicants will consider filing a terminal disclaimer, if the rejection is maintained when one or more claims in the instant application are in a condition for allowance. In view of the foregoing remarks, the applicants have noted the provisional rejection by the examiner.

VI. CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action such action is hereby solicited. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,
PILLSBURY WINTHROP SHAW PITTMAN LLP

By: _____
Thomas A. Cawley, Jr. Ph.D.
Reg. No. 40944
Tel. No. (703) 905-2144
Fax No. (703) 905-2500

TAC/PAJ/wks
P.O. Box 10500
McLean, VA 22102
(703) 905-2000

Marked up version of drawing

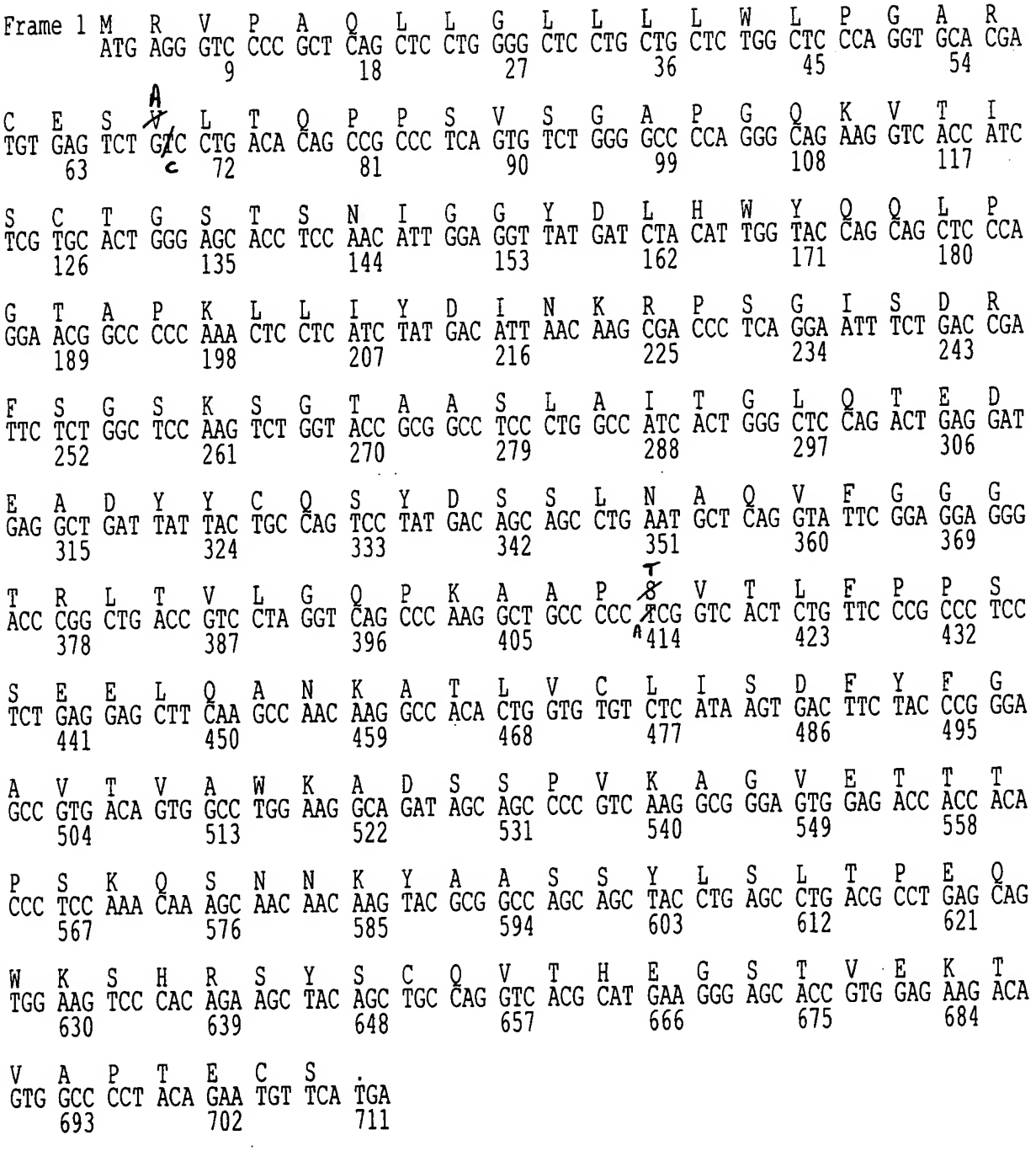

FIG. 5A